ATSDR

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Case Studies in Environmental Medicine

5

Arsenic Toxicity

Environmental ALERT . . .

- ☑ ***Except in the electronics industry, the commercial use of arsenic is declining.***
- ☑ ***Skin lesions, peripheral neuropathy, and anemia are hallmarks of chronic arsenic ingestion.***
- ☑ ***Arsenic is strongly associated with lung and skin cancer in humans, and may cause other cancers as well.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. The Agency for Toxic Substances and Disease Registry (ATSDR) and the Centers for Disease Control (CDC) designate this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association and 0.1 continuing education units for other health professionals. See pages 25 to 27 for further information.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
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How to use this issue...

This issue begins with a composite case study tha[redacted]s description is followed by a pretest. The case study is further developed through Challenge questions at the end of each section. To fully benefit from this monograph, readers are urged to answer each question when it is presented. (Answers to the Pretest and Challenge questions are found on pages 22-24.) The monograph ends with a posttest, which can be submitted to ATSDR for continuing medical education (CME) credit or continuing education units (CEU). See page 25 for further instructions on how to receive these credits.

The objective of this monograph on arsenic is to help you:

- ❑ **Understand why arsenic remains a hazard of great concern**
- ❑ **Understand the known factors contributing to arsenic poisoning**
- ❑ **Assess a patient's environmental or occupational exposure to arsenic**
- ❑ **Effectively evaluate and manage arsenic-exposed patients**
- ❑ **Utilize a variety of sources to locate further information on arsenic**

Contents

This issue is prepared with the assistance of those who share a common concern for physician education, public health, and the environment, including the following organizations: American Academy of Family Physicians (AAFP), American Academy of Pediatrics (AAP), American College of Emergency Physicians (ACEP), American College of Occupational Medicine (ACOM), American Medical Association (AMA), Association of State and Territorial Health Officials (ASTHO), and the Society of Teachers of Family Medicine (STFM). Final responsibility for the contents and views expressed in this monograph resides with ATSDR.

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Case Study

A 35-year-old carpenter with peripheral neuropathy and skin lesions

A 35-year-old, fair-skinned male is referred to your clinic for evaluation. His symptoms began approximately 3 months ago, with the insidious onset of numbness and tingling in his toes and fingertips, progressing slowly in the ensuing weeks to involve the feet and hands in a symmetric "stocking-glove" fashion. In the past 2 to 3 weeks, the tingling has taken on a progressively painful, burning quality and he has noted weakness in gripping tools. No ataxia, dysphagia, visual symptoms, or bowel or bladder incontinence have been noted, and he has not complained of headaches, back or neck pain, or confusion. Except as noted, the review of systems is otherwise negative.

The patient's medical history is remarkable for a flu-like illness approximately 4 months ago characterized by 3 to 4 days of fever, cough, diarrhea, and myalgias, which resolved spontaneously.

Further questioning reveals the patient has been a carpenter since completing high school 17 years ago. For the last 10 years, he has lived in a rural, wooded area in a home he built. Approximately 10 months ago he was married and moved with his wife, an elementary school teacher, into a newly built home on an adjacent parcel of land. The patient consumes one to two alcoholic drinks a week, and quit smoking 2 years ago after a 15-pack-year history. He takes one multivitamin a day but no prescription medications. Family history is unremarkable; his wife, parents, and two younger brothers are in good health.

Neurologic examination reveals diminished proprioception in the hands and feet, with a hyperesthetic response to pinprick sensation on the soles. Motor bulk and tone are normal, but there is slight bilateral muscular weakness in dorsiflexors of the toes and ankles, wrist extensors, and hand intrinsics. Reflexes are absent at the ankles and 1+ at the biceps and knees. Coordination and cranial nerve function are within normal limits. Dermatologic examination reveals brown patches of hyperpigmentation, with scattered overlying pale spots in and around the axillae, groin, nipples, and neck. The palms and soles show multiple hyperkeratotic corn-like elevations 4 to 10 mm in diameter. Three irregularly shaped, sharply demarcated, erythematous, scaly plaques, measuring 2 to 3 cm, are noted on the patient's torso. The remainder of the physical examination is normal.

On initial laboratory evaluation, the CBC shows slight macrocytic anemia with hematocrit 35% (normal range 40% to 52%), and MCV 111 fL (normal range 80 to 100 fL). White blood cell count is 4.3 x $10^3/mm^3$ (normal range 3.9 to 11.7 x $10^3/mm^3$); the differential reveals moderate elevation of eosinophils at 9% (normal range 0% to 4%). Occasional basophilic stippling is noted on the peripheral smear. Liver transaminases are slightly elevated. BUN, creatinine, and urinalysis are normal.

(a) What problem list is suggested for this patient?

(b) What further investigations would you undertake at this time?

(c) What treatment options would you consider?

Answers to Pretest questions can be found in Challenge answers (2) through (10) on pages 23-24.

Exposure Pathways

- **Environmental sources of arsenic exposure are food, water, and air.**
- **The relative toxicity of an arsenical depends primarily on its chemical type, valence state, solubility, and physical form.**
- **Except in the semiconductor industry, commercial use of arsenic has been declining since the 1960s.**

Arsenic is ubiquitous in the environment. It is released into the air by volcanoes, through weathering of arsenic-containing minerals and ores, and by commercial or industrial processes. In industry, arsenic is a byproduct of the smelting process for many metal ores such as lead, gold, zinc, cobalt, and nickel. Other potential sources of arsenic exposure are the following:

Natural Sources
Arsenic-containing mineral ores
Groundwater (especially near geothermal activity)

Commercial Products
Wood preservatives
Pesticides
Herbicides (weed killers, defoliants)
Fungicides
Cotton desiccants
Cattle and sheep dips
Paints and pigments
Anti-fouling paints
Leaded gasoline
Fire salts (multicolored flame)

Food
Wine (grapes sprayed with arsenic-containing pesticides)
Tobacco (plants sprayed with arsenic-containing pesticides)
Seafood (especially bivalves, certain cold water and bottom-feeding finfish, seaweed)

Industrial Processes
Purifying industrial gases (removal of sulfur)
Burning fossil fuels
Burning wood treated with arsenic preservatives
Electronics manufacturing (microwave devices, lasers, light-emitting diodes, photoelectric cells, semiconductor devices)
Hardening metal alloys
Preserving animal hides
Bronze plating
Clarifying glass and ceramics

Medicinals
Fowler's solution
Antiparasitic drugs (carbasone)
Donovan's solution
Folk remedies ("Asiatic pill," *kushtay*, yellow root)
Kelp-containing health foods
Some naturopathic remedies

Arsenic exists in three common valence states: the metalloid (0 oxidation state), arsenite (trivalent state), and arsenate (pentavalent state). Arsenic-containing compounds vary in their toxicity to mammals, depending on valence state, whether it is in the inorganic or organic form, physical state–gas, solution, or powder–and factors such as solubility, particle size, rates of absorption and elimination, and presence of impurities. With few exceptions, inorganic arsenic is more toxic than organic arsenic. The toxicity of trivalent arsenite is typically greater than that of pentavalent arsenate, but little is known about the toxicity of zero valent arsenic. Arsine gas (AsH_3), used mainly in the microelectronics industry, produces a clinical syndrome very different from other arsenic compounds and is the most toxic arsenical.

Until the 1940s, arsenicals (Salvarsan and Fowler's solution) were widely used in the treatment of various diseases such as syphilis and psoriasis. Arsenicals are still used as antiparasitic agents in veterinary medicine, and, in some countries, they are occasionally used to treat trypanosomiasis and amebiasis in humans. Arsenic is also found in some homeopathic and naturopathic preparations, and in folk remedies such as *kushtay*, a tonic used in Asian cultures to cure various sexual disorders.

Commercial use of arsenic peaked in the 1960s and since then has steadily declined. As of 1987, 74% of the arsenic used in the United States is for wood preservation, as compared to less than 1% for semiconductor manufacture. However, commercial use of arsenic in the microelectronics industry is increasing rather than declining. Gallium arsenide (GaAs) is used in integral components of discrete microwave devices, lasers, light-emitting diodes, photoelectric chemical cells, and semiconductor devices. The use of arsine gas (AsH_3) as a dopant in the production of semiconductors is also expected to increase, although substitutes of lower toxicity such as tributylarsine have recently been used. A source of arsine exposure is accidental release while manufacturing, transporting, or using the gas. More often, however, arsine forms unexpectedly when acid or other reducing substances are added to arsenic-containing compounds, such as metals in which arsenic is a low-level contaminant.

In the general population, the main route of arsenic exposure is via ingestion of arsenic-containing food and water. It has been estimated that the average daily dietary intake of arsenic by adults in the United States is 50 micrograms (µg) per day (range of 8 to 104 µg), of which about 18 µg is inorganic arsenic. Meat, fish, and poultry account for 80% of dietary arsenic intake. Fish, seafood, and algae also contain high concentrations of arsenic in the form of arsenobetaine and arsenocholine, sometimes referred to as "fish arsenic." Fish arsenic has low toxicity to humans and is rapidly excreted in urine. Wine made from grapes sprayed with arsenic-containing pesticides may have appreciable levels of arsenic. Smokers may also inhale small amounts of arsenic as a result of pesticide residue on tobacco leaves.

Well water contaminated by natural sources such as arsenic-containing bedrock has been reported to be the cause of arsenic toxicity throughout the world, including areas of the United States, Germany, Argentina, Chile, Taiwan, and the United Kingdom. The areas in the United States with the highest natural groundwater concentrations of arsenic are the Southwest, Northwest, Alaska, and other areas near geothermal activity. Groundwater may also contain elevated concentrations of arsenic due to contamination from arsenical pesticide runoff. A study con-

ducted in 1970 reported that up to 1% of community water supplies in the United States had arsenic concentrations exceeding 10 ppb. (The U.S. Environmental Protection Agency's [EPA] proposed maximum contaminant level for arsenic in drinking water is 50 parts per billion [ppb].) Both the trivalent and pentavalent forms of inorganic arsenic can be found in drinking water.

(1) The patient described in the case study lives in the wooded foothills of the Cascade range in northwest Washington. His activities have consisted mainly of building new wood frame housing, with occasional renovation of older structures. He has used lumber from these projects to fuel the stove and fireplaces in his home. Drinking water is obtained from an artesian well located on his property.

What are the potential sources of arsenic exposure for the patient described in the case study?

_____

_____

_____

(2) What steps can be undertaken to identify sources of the patient's arsenic exposure?

_____

_____

_____

Who's At Risk

- **Workers in industries producing or using arsenic-containing compounds are potentially at risk.**
- **Persons whose water supply contains high levels of arsenic or those living near sources of high ambient air levels of arsenic are at increased likelihood of exposure.**

The quantity of arsenic released by human activities exceeds amounts released from natural sources at least threefold. The major sources of arsenic release to the environment are smelters and pesticides. Besides refinery workers and farmers, other workers at increased risk of arsenic exposure include those in the industries listed on page 2. People living near smelters and other arsenic-emitting facilities also have potential risk of exposure from fugitive airborne emissions and groundwater contamination.

Arsenic is notorious as a poison because white arsenic (arsenic trioxide) has no odor or taste and is available in inexpensive products such as pesticides. Most arsenic poisonings are due to unintentional ingestion by children. In 1989, EPA instituted a phaseout of certain arsenic-containing ant poisons in an effort to reduce the incidence of children's arsenic ingestion.

Burning plywood treated with an arsenate wood preservative in a poorly ventilated cabin has been blamed for poisoning a family in rural Wisconsin. Green wood or pressed wood treated with copper arsenate to prevent mildew is commonly used in marine applications, patio decks, and recreational structures for children's playgrounds. Cutting this wood or erosion of the veneer may lead to arsenic exposure. Children who play on wood structures treated with copper arsenate have increased likelihood of dermal contact or ingestion of the arsenical through normal mouthing and play activities.

Methyl transferase enzymes play a necessary role in the methylation of arsenic in mammals. The effect of dietary deficiencies and genetic variability on methylating capacity may have important implications for tissue distribution and individual susceptibility to arsenic toxicity. Experimental animals fed protein-deficient diets while exposed to high levels of arsenic have shown a decreased methylating capacity, which has led to increased deposits of arsenic in liver, lung, and other organ sites, and presumably increased susceptibility to arsenic toxicity.

Arsenic can cross the placenta, exposing the fetus. Significant levels of arsenic were found in an infant born 4 days after the mother ingested arsenic in a suicide attempt. Increased incidence of spontaneous abortions, infant congenital malformations, and decreased birth weights have been reported among women and their offspring living near a smelter in Sweden; however, it is not clear that these events can be ascribed to arsenic alone.

- **Arsenic can cross the placenta, increasing the likelihood of exposure to the fetus.**

Biologic Fate

In humans, soluble forms of ingested arsenic are well absorbed from the gastrointestinal tract (60% to 90%). The amount of arsenic absorbed by inhalation has not been determined precisely, but is thought to be in this range. Dermal absorption is generally negligible, although toxic systemic effects have resulted from rare occupational accidents where either arsenic trichloride or arsenic acid was splashed on workers' skin. Airborne arsenic in the workplace is generally in the form of arsenic trioxide. Its particle size determines whether arsenic will reach

- **The primary routes of arsenic entry into the human body are ingestion and inhalation; percutaneous absorption has been reported in occupational settings.**
- **Most tissues rapidly clear arsenic except for skin, hair, and nails.**

- **Arsenic undergoes biomethylation to less toxic metabolites in the liver.**
- **Arsenic is excreted in the urine; most of a single, low-level dose is excreted within a few days after ingestion.**

the lower respiratory tract or be deposited in the upper airways and be swallowed after mucociliary clearance. Autopsies performed on retired smelter workers show that arsenic-containing particles may remain in the lungs for years.

After absorption through the lungs or gastrointestinal tract, arsenic initially accumulates in the liver, spleen, kidney, lungs, and gastrointestinal tract. Clearance from these tissues, however, is rapid. Two to 4 weeks after exposure ceases, most of the arsenic remaining in the body is found in keratin-rich tissues such as skin, hair, and nails, and to a lesser extent, in bones and teeth.

Oxidation-reduction reactions result in some interconversion of arsenate (+5) and arsenite (+3) *in vivo*. A portion of the arsenite is then biomethylated, predominantly in the liver, to methylarsonic acid and dimethylarsinic acid. The methylation process may represent detoxification because the metabolites exert less acute toxicity in experimental lethality studies.

Methylation efficiency in humans decreases with increasing arsenic dose. When the methylating capacity of the liver is exceeded, exposure to excess levels of inorganic arsenic results in increased retention of arsenic in soft tissues. Cell culture studies suggest that the methylating process is inducible since pretreatment with small amounts of arsenic over a prolonged period increases the methylating efficiency when a large dose is subsequently applied. Fish arsenic is apparently not biotransformed *in vivo*, but is rapidly excreted unchanged in the urine.

Arsenic is excreted primarily through the kidneys. After low-level exposure to inorganic arsenic, most of the urinary arsenic is present as methylated metabolites. Other less important routes of elimination of inorganic arsenic include sweat, skin desquamation, and incorporation into hair and nails.

After a single intravenous injection of radiolabeled trivalent inorganic arsenic in human volunteers, most of the arsenic cleared through urinary excretion within 2 days, although a small amount of arsenic was found in the urine up to 2 weeks later. The biologic half-life of ingested fish arsenic in humans is estimated to be less than 20 hours, with total clearance in approximately 48 hours. Because arsenic is rapidly cleared from the blood, blood levels may be normal even when urine levels remain markedly elevated.

Challenge

(3) Analysis of a spot sample of the patient's urine revealed 6000 µg/L (normal is less than 50 µg/L) as total arsenic. What factors could be responsible for this level, and what additional history would you elicit?

Physiologic Effects

Two mechanisms of arsenic toxicity that may lead to injury in a number of organ systems have been described. It is believed that arsenic's overt toxicity results primarily from its inhibition of critical sulfhydryl-containing enzymes; trivalent arsenite is particularly potent in this regard. Pentavalent arsenate, however, can competitively substitute for phosphate in many biochemical reactions. Replacing the stable phosphate anion with the less stable arsenate anion leads to rapid hydrolysis of the high-energy bonds in compounds such as ATP. Loss of these bonds results in the loss of energy needed for critical steps in cellular metabolism.

Arsine gas poisoning results in a considerably different syndrome from that caused by other forms of arsenic. After inhalation, arsine rapidly fixes to red cells, producing irreversible cell membrane damage. At low levels arsine is a potent hemolysin, causing dose-dependent intravascular hemolysis. At high levels arsine produces direct multisystem cytotoxicity.

- **Because it targets ubiquitous enzyme reactions, arsenic affects nearly all organ systems.**
- **Unlike other arsenicals, arsine gas causes a hemolytic syndrome.**
- **Arsenic is strongly associated with lung and skin cancers and may cause other cancers.**

Gastrointestinal, Hepatic, and Renal Effects

The gastrointestinal effects of arsenic are generally the result of ingestion; however, GI effects may also occur after heavy exposure by other routes. The fundamental GI lesion appears to be increased permeability of the small blood vessels, leading to fluid loss and hypotension. Extensive inflammation and necrosis of the mucosa and submucosa of the stomach and intestine

- **Gastrointestinal effects are seen primarily after arsenic ingestion, and less often after inhalation or dermal absorption.**

- **Acute arsenic toxicity may be associated with hepatic necrosis and elevated levels of liver enzymes.**
- **Arsenic is capable of causing acute renal failure, as well as chronic renal insufficiency.**

may occur and progress to perforation of the gut wall. A hemorrhagic gastroenteritis may develop, with bloody diarrhea as a presenting symptom.

Arsenic intoxication may also result in hepatic effects, including elevated liver enzyme levels. Autopsies of Japanese children poisoned with arsenic-contaminated milk revealed hepatic hemorrhagic necrosis and fatty degeneration of the liver. Chronic arsenic ingestion may lead to noncirrhotic portal hypertension. Case reports have also linked chronic high-level arsenic exposure with hepatic angiosarcoma, a rare form of cancer.

The systemic toxicity occurring in severe acute arsenic poisoning may be accompanied by acute renal tubular necrosis. Glomerular damage can result in proteinuria. Cortical necrosis has also been reported.

Cardiovascular Effects

- **Acute arsenic poisoning may cause both diffuse capillary leak and cardiomyopathy, resulting in shock.**
- **Long-term ingestion of arsenic in drinking water has resulted in pronounced peripheral vascular changes.**

The extent of cardiovascular injury may vary with age, arsenic dose, and individual susceptibility. In acute arsenic poisoning–usually suicide attempts–the fundamental lesion, diffuse capillary leak, leads to generalized vasodilation, transudation of plasma, hypotension, and shock. Delayed cardiomyopathy may also develop. Myocardial damage can result in a variety of electrocardiographic findings including broadening of the QRS complex, prolongation of the QT interval, ST depression, flattening of T waves, and atypical, multifocal ventricular tachycardia.

Epidemiologic evidence indicates that chronic arsenic exposure is associated with vasospasm and peripheral vascular insufficiency. Gangrene of the extremities, known as Blackfoot disease, has been associated with drinking arsenic-contaminated well water in Taiwan, where the prevalence of the disease increased with increasing age and well-water arsenic concentration (10 to 1820 ppb). Persons with Blackfoot disease also had a higher incidence of arsenic-induced skin cancer. However, investigators believe other vasoactive substances found in the water may have been contributory.

Raynaud's phenomenon and acrocyanosis resulted from contamination of the city's drinking water supply in Antofagasta, Chile, at arsenic concentrations ranging from 20 to 400 ppb. Autopsies of Antofagasta children exposed to arsenic revealed fibrous thickening of small- and medium-sized arteries and myocardial hypertrophy. Similar vascular disorders, as well as abnormal electrocardiographs (ECGs), have been noted in vineyard workers exposed to arsenical pesticides.

Neurologic Effects

- **Arsenic-exposed patients develop destruction of axonal cylinders leading to peripheral neuropathy.**

Peripheral neuropathy is a common complication of arsenic poisoning. It is predominantly due to destruction of axonal cylinders (axonopathy). Early electrodiagnostic testing may reveal features indistinguishable from Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy). The neuropathy evolves into a more classic sensorimotor distal axonopathy. Sensory effects, particularly painful dysesthesia, occur earlier and may predominate in moderate poisoning, whereas ascending weakness and paralysis may predominate in severe poisoning. However, cranial nerves are rarely affected, even in severe poisoning. Both acute and chronic arsenic intoxication may be associated with encephalopathy.

Recovery from neuropathy induced by chronic exposure to arsenic compounds is generally slow, sometimes taking years, and complete recovery may not occur. Follow-up studies of Japanese children who chronically consumed arsenic-contaminated milk revealed an increased incidence of severe hearing loss, mental retardation, epilepsy, and other brain damage. Hearing loss as a sequelae of acute or chronic arsenic intoxication has not been confirmed by other case reports or epidemiologic studies.

Dermal Effects

- **Pigment changes and palmoplantar hyperkeratosis are characteristic of chronic arsenic exposure.**
- **Benign arsenical keratoses may progress to malignancy.**

The skin lesions occurring most frequently in arsenic-exposed humans are hyperpigmentation, hyperkeratosis, and skin cancer. Patchy hyperpigmentation, a pathologic hallmark of chronic exposure, may be found anywhere on the body, but occurs particularly on the eyelids, temples, axillae, neck, nipples, and groin. The classic appearance of the dark brown patches with scattered pale spots is sometimes described as "raindrops on a dusty road." In severe cases, the pigmentation extends broadly over the chest, back, and abdomen. Pigment changes have been observed in populations chronically consuming drinking water containing 400 ppb or more arsenic.

Arsenical hyperkeratosis occurs most frequently on the palms and soles. Keratoses usually appear as small corn-like elevations, 0.4 to 1 centimeter in diameter. In most cases, arsenical keratoses show little cellular atypia and may remain morphologically benign for decades. In other cases, cells develop marked atypia (precancerous) and appear indistinguishable from Bowen's disease, which is an *in situ* squamous cell carcinoma discussed in Carcinogenic Effects below.

Respiratory Effects

- **Inhalation of high concentrations of arsenic compounds produces irritation of the respiratory mucosa.**
- **Lung cancer has been reported in populations of arsenic-exposed smelter workers.**

Smelter workers experiencing prolonged exposures to high concentrations of airborne arsenic at levels rarely found today had inflammatory and erosive lesions of the respiratory mucosa, including nasal septum perforation. Lung cancer has been associated with chronic arsenic exposure in smelter workers and pesticide workers.

Hematopoietic Effects

- **Bone marrow depression may result from acute or chronic arsenic intoxication and may initially manifest as pancytopenia.**

Both acute and chronic arsenic poisoning may affect the hematopoietic system. A reversible bone marrow depression with pancytopenia may occur. Anemia and leukopenia are common in chronic arsenic toxicity and are often accompanied by thrombocytopenia and mild eosinophilia. The anemia may be normocytic or macrocytic, and basophilic stippling may be noted on peripheral blood smear.

Carcinogenic Effects

- **The carcinogenicity of arsenic in humans has been established, but no animal model has been developed.**

In humans, chronic arsenic ingestion is strongly associated with an increased risk of skin cancer, and may cause cancers of the lung, liver, bladder, kidney, and colon; chronic inhalation of arsenicals has been closely linked with lung cancer. The precise mechanism of arsenic-related carcinogenicity is unknown. Arsenic causes chromosomal damage in cultured mammalian cells, which may be mediated by arsenic's effects on the enzymatic processes involved in DNA replication and repair. Paradoxically, cancer associated with arsenic exposure has not been produced in experimental animals.

Skin Cancer

- **Latency for skin cancer associated with ingestion of arsenic may be 3 to 4 decades, while the noncarcinogenic skin effects typically develop several years after exposure.**

An increased risk of skin cancer in humans is associated with chronic exposure to inorganic arsenic in medication, contaminated water, and the workplace. Arsenic-induced skin cancer is frequently characterized by lesions over the entire body, mostly in unexposed areas such as the trunk, palms, and soles. More than one type of skin cancer may occur in a patient. Most of the Taiwanese who developed skin cancer in association with ingested arsenic-contaminated drinking water had multiple cancer types. The most commonly reported types, in order of decreasing frequency, were intraepidermal carcinomas (Bowen's disease), squamous cell carcinomas, basal cell carcinomas, and "combined forms." Seventy-two percent of the Taiwanese with skin cancer also had hyperkeratosis, and 90% had hyperpigmentation.

Some hyperkeratinized lesions can develop into intraepidermal carcinoma, which may ultimately become invasive. The lesions are sharply demarcated, round or irregular plaques that tend to enlarge; they may vary in size from 1 mm to more than 10 cm. Arsenical basal cell carcinomas most often arise from normal tissue, are almost always multiple, and frequently occur on the trunk. The superficial spreading lesions are red, scaly, atrophic, and are often indistinguishable from Bowen's disease by clinical examination. Arsenic-associated squamous cell carcinomas are distinguished from uv-induced squamous cell carcinomas by their tendency to occur on the extremities (especially palms and soles) and trunk rather than on sun-exposed areas such as the head and neck.

Epidemiologic studies indicate that a dose-response relationship exists between the level of arsenic in drinking water and the prevalence of skin cancers in the exposed population. Excessive mortality rates due to arsenic-induced skin cancer have also been observed in vineyard workers with dermal and inhalation exposure.

Lung Cancer

An association between lung cancer and occupational exposure to inorganic arsenic has been confirmed in several epidemiologic studies. A higher risk of lung cancer was found among workers exposed predominantly to arsenic trioxide in smelters and to pentavalent arsenical pesticides in other settings. Neither concomitant exposure to sulfur dioxide nor cigarette smoke were determined to be essential co-factors in these studies.

- **In arsenic-exposed workers, there is a systematic gradient in lung cancer mortality rates, depending upon duration and intensity of exposure.**

Clinical Evaluation

History and Physical Examination

The source of exposure is identified in fewer than 50% of arsenic poisonings; however, a careful history and physical examination may improve these statistics. Because arsenic intoxication may affect multiple organ systems, a complete physical examination is imperative. In chronic ingestion, particular clues to arsenic

- **The source of arsenic exposure cannot be identified in many cases.**

poisoning may be provided by dermatologic and neurologic findings. The medical history should include the following:

- occupational history
- diet
- residential history (proximity to smelters, other industry, and hazardous waste sites)
- smoking history
- condition of household pets
- hobbies (including use of pesticides or herbicides in farming or gardening)
- medications (including folk or naturopathic medications)
- source of drinking water
- home heating methods (wood-burning stoves and fireplaces)

Signs and Symptoms

Acute Exposure

- **In acute arsenic poisoning, death is usually due to cardiovascular collapse and hypovolemic shock.**
- **Onset of peripheral neuropathy may be delayed several weeks after the initial toxic insult.**
- **Mees lines may be visible in the fingernails several months after acute arsenic exposure.**

Acute arsenic poisoning rarely occurs in the workplace today; it usually results from unintentional ingestion, suicide, or homicide. The fatal dose of ingested arsenic in humans is difficult to determine from case reports and depends upon many factors (e.g., solubility, valence state, etc.). The minimal lethal dose is in the range of 50 to 300 milligrams. The signs and symptoms of acute arsenic poisoning include the following:

Gastrointestinal

- severe abdominal pain
- nausea and vomiting
- bloody or rice-water diarrhea

Cardiovascular and Respiratory

- hypotension, shock
- ventricular arrhythmia
- pulmonary edema

Neurologic

- light-headedness
- headache
- weakness, lethargy
- delirium
- encephalopathy
- convulsions
- coma
- sensorimotor peripheral neuropathy

Hepatic and Renal

- elevated liver enzymes
- hematuria, oliguria, proteinuria,
- acute tubular necrosis, renal cortical necrosis

Hematologic

- anemia
- leukopenia
- thrombocytopenia
- disseminated intravascular coagulation

Other

- rhabdomyalysis
- garlic odor on the breath
- delayed appearance of Mees lines

As a result of inorganic arsenic's direct toxicity to the epithelial cells of the gastrointestinal tract and its systemic enzyme inhibition, profound gastroenteritis, sometimes with hemorrhage, can occur within minutes to hours after acute ingestion. Symptoms may last for several days. Difficulty in swallowing, abdominal pain, vomiting, diarrhea, and dehydration may result. However, in subacute poisoning the onset of milder GI symptoms may be so insidious that the possibility of arsenic intoxication is overlooked.

Arsenic has deleterious effects on the heart and peripheral vascular system. Capillary dilation with fluid leakage and third spacing may cause severe hypovolemia and hypotension. Cardiac manifestations have included cardiomyopathy, ventricular dysrhythmias (atypical ventricular tachycardia and ventricular fibrillation), and congestive heart failure.

A delayed sensorimotor peripheral neuropathy may occur after acute arsenic poisoning. Symptoms are initially sensory and may begin 2 to 4 weeks after resolution of the first signs of intoxication resulting from ingestion (shock or gastroenteritis). Commonly reported initial symptoms include numbness, tingling and "pins and needles" sensations in the hands and feet in a symmetrical "stocking-glove" distribution, and muscular tenderness in the extremities. Clinical involvement spans the spectrum from mild paresthesia with preserved ambulation to distal weakness, quadriplegia, and, in rare instances, respiratory muscle insufficiency.

Other findings in acute arsenic poisoning may include fever and facial edema. Several months after poisoning, transverse white striae (pale bands) on the nails called Mees lines (or Aldrich-Mees lines) may be seen, reflecting transient disruption of nail plate growth during acute poisoning. In episodes of multiple acute exposures, several Mees lines may occur within a single nail. In some cases, the distance of the lines from the nail bed may be used to roughly gauge the date of the poisoning episode.

Respiratory tract irritation (cough, laryngitis, mild bronchitis, and dyspnea) may result from acute exposure to airborne arsenic dust. Nasal septum perforation, as well as conjunctivitis and dermatitis, have also been reported.

The toxicity of arsine gas is quite different from toxicity of other arsenicals, requiring different emphases in the medical history, physical examination, and patient management. Arsine is a powerful hemolytic poison in both acute and chronic exposures. The clinical signs of hemolysis may not appear for up to 24 hours after acute exposure, thereby obscuring the relationship between exposure and effect. Initial symptoms of arsine poisoning may include headache, nausea, abdominal pain, and hematuria.

Chronic Exposure

- **Neuropathy may be the first sign of chronic arsenic toxicity.**
- **Hyperpigmentation and hyperkeratosis are delayed hallmarks of chronic arsenic exposure.**
- **Anemia often accompanies skin lesions in patients chronically poisoned by arsenic.**
- **Lung cancer and skin cancer are serious long-term concerns in cases of chronic arsenic exposure.**

Skin lesions and peripheral neuropathy are the most suggestive effects of arsenic ingestion, and their presence should result in an aggressive search for this etiology. Neuropathy can occur insidiously in chronic toxicity without other apparent symptoms. However, careful evaluation usually reveals signs of multiorgan and multisystem involvement such as anemia, leukopenia, skin changes, or elevated liver function tests.

Manifestations of chronic arsenic ingestion depend on both the intensity and duration of exposure. An intense exposure of several milligrams a day results in anemia, neuropathy, and hepatotoxicity within a few weeks to months. Hematologic and neurologic signs may occur after a similar latency period. Skin lesions, however, take longer to manifest (3 to 7 years for pigmentation changes and keratoses; up to 40 years for skin cancer) and may occur after lower doses than those causing neuropathy or anemia.

Chronic arsenic dust inhalation may be accompanied by upper respiratory symptoms, nasal perforation, and lung cancer; however, since permissible workplace arsenic levels have been lowered, these conditions are rarely encountered in workers.

(4) What findings are suggestive of arsenic intoxication in the patient described in the case study?

_____

_____

(5) What conditions other than arsenic intoxication should be considered in the differential diagnosis of the patient's neurological complaints?

_____

_____

Laboratory Tests

Clinical diagnosis of arsenic intoxication is often difficult because both acute and chronic poisoning present a wide spectrum of signs and symptoms, which are largely dependent upon route of exposure, chemical form, dose, and time elapsed since exposure. In many cases, the patient or person providing the history may suppress information, or the source of exposure may not be apparent. By integrating laboratory results with history and clinical findings, it is often possible to confirm a diagnosis.

Early clinical diagnosis of arsenic toxicity is often difficult; a key laboratory test in recent exposures is urinary arsenic excretion.

Immediately after patient stabilization, laboratory tests should be performed to obtain baseline values, with periodic monitoring as indicated. Because urinary levels of arsenic may drop rapidly in the first 24-48 hours after acute exposure, a urine specimen for arsenic analysis should be obtained promptly. Depending on the patient's clinical state, tests may include the following:

General Tests

- CBC with peripheral smear
- Liver function tests
- BUN and creatinine
- Urinalysis
- Nerve conduction velocity (if peripheral neurologic symptoms are present)
- ECG
- Chest X ray
- Bone marrow biopsy

Specific Tests

- Urine arsenic concentration

Some arsenic compounds, particularly those of low solubility, are radiopaque, and if ingested may be visible on an abdominal radiograph.

Direct Biologic Indicators

The key diagnostic laboratory test for recent exposure is urinary arsenic measurement. The best specimen is a 24-hour urine collection, although spot urine specimens can be helpful in an emergency. Normal total urinary arsenic values are less than 50 µg arsenic per liter (As/L) in the absence of consumption of seafood in the past 48 hours; values in excess of 200 µg As/L are considered abnormal. Test results may be reported in µg arsenic per gram creatinine to avoid effects due to variation in urine output. Fish arsenic can significantly increase total urinary arsenic levels; therefore, it may be prudent to take a dietary history of the previous 48 hours or repeat the urinary arsenic test in 2 or 3 days. Human volunteers with an average pretest urinary

When total urinary arsenic is measured, it is important to inquire about recent diet.

arsenic level of 30 µg/L were given lobster tail for lunch. Four hours after eating, they had an average urinary level of 1300 µg As/L. These values decreased to pretest levels within 48 hours after ingestion. Arsenic blood levels, normally less than 7 µg/dL, are less useful than urinary arsenic measurements in following the clinical course of an acute poisoning case because of the rapid clearance of arsenic from the blood.

Long after urine levels have returned to baseline, the arsenic content of hair and nails may be the only clue of arsenic exposure. However, because the arsenic content of hair and nails may be increased by external contamination, caution must be exercised in using the arsenic content of these specimens to diagnose arsenic intoxication.

Indirect Biologic Indicators

The standard tests listed above will aid in evaluating the status of an arsenic-exposed patient. The CBC can provide evidence of arsenic-induced anemia, leukopenia, thrombocytopenia, or eosinophilia. Although basophilic stippling on the peripheral smear does not confirm arsenic poisoning, it is consistent with the diagnosis. Liver transaminases are frequently elevated in acute and chronic arsenic exposure and can help confirm clinical suspicion. If arsenic neuropathy is suspected, nerve conduction velocity tests should be performed. Such tests may show a decrease in amplitude initially, as well as slowed conduction. Skin lesions in patients with chronic arsenic exposure may require biopsy to rule out skin cancer.

Challenge

(6) What further medical work-up is indicated for the patient described in the case study?

_____

(7) What does the presence of palmar-plantar keratosis suggest about the time course of the patient's arsenic exposure?

_____

(8) Who else in the case study is at risk for exposure to arsenic?

_____

(9) A urine specimen from the wife of the patient was found to contain total arsenic at a concentration of 300 µg/L, and a sample of the wife's hair contained 150 ppm arsenic. Compare this to the patient's 6000 µg/L urinary arsenic level and 100 ppm arsenic in the hair. The wife has no signs or symptoms of chronic arsenic intoxication. How might these findings be explained?

_____

_____

Treatment and Management

Acute Exposure

Patients with suspected acute arsenic poisoning generally require rapid stabilization with fluid and electrolyte replacement in an intensive-care setting. Aggressive intravenous fluid replacement therapy may be life-saving in severe acute poisoning. Gastric lavage may be useful soon after an acute ingestion to prevent further absorption. The efficacy of activated charcoal is controversial, but its administration together with a cathartic (such as sorbitol) is frequently recommended. If profuse diarrhea is present, cathartics should be withheld. Hemodialysis may be beneficial in a patient with concomitant renal failure.

- **Gut decontamination and hemodynamic stabilization are key factors in the initial management of acute arsenic intoxication.**
- **Chelating agents administered within hours of arsenic absorption may successfully prevent the full effects of arsenic toxicity.**

Dimercaprol (2,3-dimercaptopropanol, also known as British anti-Lewisite or BAL) is the most frequently recommended chelating agent for arsenic. Parenteral dimercaprol is often administered intramuscularly at an initial dose of 3 to 5 milligrams per kilogram of body weight every 4 hours for 2 days, and every 6 hours on the third day, then every 12 hours thereafter for 10 days, unless an orally administered chelating agent is substituted. Data supporting duration of treatment are limited, and regimens may warrant adjustment. If acute renal insufficiency develops, hemodialysis may be of value in removing the dimercaprol-arsenic complex. Since certain dimercaprol-metal complexes are less stable in acid media, alkalization of the urine has been recommended to protect the kidneys during therapy. All known chelating agents have adverse side effects and should be used with caution.

In animal models, the efficacy of chelation therapy generally declines as the time elapsed since exposure increases. If patients are treated within several hours after arsenic ingestion, chelation is likely to be beneficial. Therefore, even if arsenic ingestion is only suspected, it may be valuable to give one or two doses of dimercaprol while awaiting confirmation since side effects usually are not noxious enough to outweigh benefits.

Another potential chelating agent is dimercaptosuccinic acid (DMSA), a water-soluble analog of dimercaprol currently under investigation. Hypotension, nausea, vomiting, and diarrhea early in the course of arsenic poisoning may hamper administration and subsequent absorption of oral DMSA. The use of D-penicillamine as an oral chelating agent is controversial.

Therapy in arsine gas poisoning is supportive and is primarily aimed at maintaining renal function. Exchange transfusion with donor cells may be necessary to replace the patient's hemolyzed red cells.

If the source of arsenic exposure has not been determined, it may be inadvisable to discharge patients until the health department or other appropriate officials have inspected their environment. Unless such inspection locates and eliminates the source of exposure, the patient may be at risk for further arsenic intoxication.

Chronic Exposure

- **Removal from the source of poisoning and supportive measures are used to manage a patient chronically poisoned with arsenic.**
- **Available evidence does not support the routine use of chelation therapy for patients with an established arsenic neuropathy.**

Identification and removal of the toxic source and supportive measures are primary concerns for the treatment of chronically exposed patients. Studies suggest that the use of vitamin A analogs (retinoids) may be useful in treating precancerous arsenical dermatoses. Recovery from chronic arsenic toxicity, particularly from the resulting peripheral neuropathy, may take months and may not be complete. An established arsenical neuropathy is not improved by chelation therapy. The value of chelation therapy in preventing an incipient neuropathy has been suggested but not adequately demonstrated.

Challenge

(10) What treatment will you recommend for the patient described in the case study?

Standards and Regulations

Workplace

Air

The Occupational Safety and Health Administration (OSHA) mandates permissible limits for occupational exposures. The permissible exposure limit (PEL) for arsenic can be no greater than 10 micrograms of inorganic arsenic per cubic meter of air (10 $\mu g/m^3$), averaged over any 8-hour period for a 40-hour workweek. The recommended exposure limit (REL) set by the National Institute for Occupational Safety and Health (NIOSH), is 2 $\mu g/m^3$ for a 15-minute ceiling, based on classification of arsenic as a potential human carcinogen (Table 1).

- **There is little agreement between governmental regulations and the recommendations of advisory organizations on the acceptable levels of arsenic in the workplace.**

Table 1. Standards and regulations for inorganic arsenic

Agency *	Focus	Level	Comments
ACGIH	Air-Workplace	200 $\mu g/m^3$	Advisory; 8-hour TWA†
NIOSH	Air -Workplace	2 $\mu g/m^3$	Advisory; 15-min ceiling limit
OSHA	Air -Workplace	10 $\mu g/m^3$	Regulation; PEL§ over 8-hour workday
EPA	Air-Environment	N/A	Under review
	Water	50 ppb	Regulation; maximum contaminant level in drinking water
FDA	Food	0.5-2 ppm	Regulation; applies to animals treated with veterinary drugs

* ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; WHO = World Health Organization

† TWA (Time-Weighted Average) = time-weighted average concentration for a normal 8-hour workday and 40-hour workweek to which nearly all workers may be repeatedly exposed.

§ PEL (Permissible Exposure Limit) = highest level averaged over an 8-hour workday, to which a worker may be exposed.

Environment

Air

- **EPA limits the emissions from copper smelters, glass manufacturing plants, and other arsenic-using facilities; however, no ambient air standard for arsenic currently exists.**

Arsenic is listed by EPA, under authorization of the Clean Air Act, as a hazardous air pollutant, defined as a substance that may cause an increased mortality or serious illness in humans after significant exposure. In 1986, EPA promulgated the National Emissions Standards for Hazardous Air Pollutants for three stationary source categories known to emit organic arsenic: primary copper smelters, glass manufacturing plants, and arsenic plants. However, there is currently no ambient air standard for arsenic.

Drinking Water

- **EPA has recently proposed 50 ppb as the allowable level for arsenic in drinking water.**

The EPA Office of Drinking Water has proposed a MCL for arsenic in drinking water of 50 ppb. The World Health Organization (WHO) also recommends a drinking water guideline of 50 ppb, which is considered to be a tenfold safety margin above levels known to have caused skin cancer in Taiwan.

Food

- **FDA currently has no tolerance levels for arsenic in food, except for the byproducts of animals treated with veterinary drugs.**

The U.S. Food and Drug Administration (FDA) has established tolerance levels for arsenic in byproducts of animals treated with veterinary drugs. These permissible levels range from 0.5 ppm in eggs and uncooked edible tissues of chickens and turkeys to 2 ppm in certain uncooked edible byproducts of swine.

Pesticides

- **In 1989, household ant killers containing sodium arsenate were banned because of danger of ingestion by small children.**

In 1989, EPA began to phase out household ant poisons containing sodium arsenate because of the danger of ingestion by small children. The EPA Office of Pesticide Programs (OPP) has restricted the use of inorganic arsenic to pressure-treating wood. It has proposed cancellation of all registered uses of inorganic arsenic for nonwood preservative purposes except for the use of calcium arsenate as a turf herbicide, lead arsenate as a grapefruit growth regulator, sodium arsenite as a grape fungicide, and arsenic acid as a crop desiccant, all of which are under review.

(11) Would it be important to notify authorities of the patient described in the case? Why?

_____

_____

Suggested Reading List

General

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Schoolmeester WL, White DR. Arsenic poisoning. South Med J 1980;2:198-208.

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Franklin M, Bean W, Harden RC. Fowler's solution as an etiologic agent in cirrhosis. Am J Med Sci 1950;219:589-96.

Hematologic Effects

Kyle RA, Pease GL. Hematologic aspects of arsenic intoxication. N Engl J Med 1965;273:18-23.

Selzer PM, Ancel MA. Chronic arsenic poisoning masquerading as pernicious anemia. West J Med 1983;139:219-20.

Drinking Water as Source of Exposure

Armstrong CW, Stroube RB, Rubio T, et al. Outbreak of fatal arsenic poisoning caused by contaminated drinking water. Arch Environ Health 1984;39:276-9.

Chen CJ, Chuang YC, You SL, Lin TM, Wu HY. A retrospective study on malignant neoplasms of bladder, lung, and liver in Blackfoot disease endemic area in Taiwan. Br J Cancer 1986;53:399-405.

Valentine JL, Kang HK, Spivey G. Arsenic levels in human blood, urine, and hair in response to exposure via drinking water. Environ Res 1979;20:24-32.

Related Government Documents

Agency for Toxic Substances and Disease Registry. Toxicological profile for arsenic. Atlanta: US Department of Health and Human Services, Public Health Service, 1989. NTIS report no. PB/89/185706/AS.

Environmental Protection Agency. Health assessment document for inorganic arsenic. Research Triangle Park, NC: US Environmental Protection Agency, Environmental Criteria and Assessment Office, 1984. Report no. EPA/600/8-83/021F.

Environmental Protection Agency. Special report on ingested inorganic arsenic: skin cancer; nutritional essentiality. Washington, DC: US Environmental Protection Agency, Risk Assessment Forum, 1988. Report no. EPA/625/3-87/013.

Answers to Pretest and Challenge Questions

(1) The patient's drinking water, obtained from an artesian well, may contain elevated levels of arsenic due to leaching from natural mineral deposits in the surrounding bedrock. This phenomenon has been noted sporadically throughout the United States, including the Northwest. The patient's employment in carpentry and home construction may place him in contact with arsenic-containing wood preservatives used to treat lumber. Exposure may potentially occur percutaneously in the course of repeatedly handling moist, freshly treated lumber or via inhalation or ingestion of wood dust liberated during sawing. Ingestion or inhalation of ash or flue gas created during burning of arsenic-treated wood in his home fireplace or wood stove may also be a source of household arsenic exposure.

(2) A sample of the patient's well water can be sent for arsenic analysis. Lists of qualified laboratories may be obtained from the county or state health department. The patient should be questioned about his use of arsenic-treated wood and wood preservatives: arsenic content may be listed on product containers or on Material Safety Data Sheets available from the supplier. The supplier should also indicate whether purchased lumber has been treated with arsenical wood preservatives. The patient should be questioned regarding possible use of arsenic-containing pesticides. In any case of suspected arsenic intoxication, the physician should consider the possibility of intentional poisoning and notify social agencies, if appropriate.

(3) Because nontoxic trimethylated organic arsenic (arsenobetaine or arsenocholine) ingested in a seafood meal may markedly elevate *total* arsenic levels, the patient should be questioned about ingestion of seafood within the past 2 days. If seafood has been ingested, laboratory speciation of the urinary arsenic can eliminate the contribution of arsenobetaine or arsenocholine. However, given the patient's clinical presentation, exposure to toxic inorganic arsenic is likely.

In this case, speciation reveals inorganic arsenic present at 1700 µg/L, monomethyl arsonic acid at 2200 µg/L, and dimethyl arsenic acid at 2100 µg/L, confirming that the patient has sustained inorganic arsenic exposure. Since most laboratories do not provide speciation, an alternative approach to interpreting a high urinary arsenic concentration (>500 to 1000 µg/L) if seafood ingestion is a possible factor would be to repeat the measurement with a new urine sample 48 to 96 hours after complete avoidance of seafood. The trimethylated fish arsenic should be completely cleared by that time, but the metabolites of inorganic arsenic, which have slower clearance, should still be present at elevated levels.

(4) The patient's problem list includes peripheral neuropathy, hyperpigmentation and hyperkeratotic skin lesions, macrocytic anemia, and liver transaminase elevation. The neurologic, dermatologic, and hematologic abnormalities are highly suggestive of chronic arsenic intoxication. He has a characteristic stocking-glove peripheral neuropathy, with predominantly painful sensory symptoms, in the absence of apparent cranial nerve or central nervous system dysfunction. His skin displays hyperpigmentation and palmar-plantar hyperkeratoses characteristic of chronic arsenic ingestion. Consistent laboratory findings include a CBC and peripheral blood smear displaying macrocytic anemia, relative eosinophilia, and occasional basophilic stippling, and a chemistry panel revealing slight elevation in liver transaminases.

(5) Guillain-Barré syndrome is a primarily motor neuropathy that may begin shortly after a viral infection or immunization. Although the patient's neurological complaints began 1 month after a flu-like illness, examination failed to reveal the characteristic rapid tempo and motor predominance of Guillain-Barré syndrome. Chronic alcoholism may be associated with sensorimotor peripheral neuropathy, macrocytic anemia, and liver transaminase elevation, but cerebellar ataxia and other findings such as hepatomegaly and telangiectasia are usually also present with alcoholism. Thallium intoxication may also result in a sensorimotor peripheral neuropathy. Other diagnostic considerations include paraneoplastic syndromes, particularly those associated with lung cancer, diabetes mellitus, and certain chronic inflammatory neuropathies.

(6) The patient's urine should be screened for the presence of arsenic and thallium using either a 24-hour urine collection or a first void morning specimen. A chest X ray should be examined for occult malignancy. Referral for electromyography and nerve conduction studies may be useful to further characterize the peripheral neuropathy and to establish an objective baseline for follow-up measurement. Dermatologic assessment of the patient's skin lesions, possibly including skin biopsy, is indicated to evaluate for cancer or to characterize a precancerous state. The possibility of diabetes mellitus can be investigated by measuring a fasting blood glucose.

(7) Arsenic-induced skin changes generally result from chronic arsenic exposure and have a latency of several years. Hyperpigmentation typically precedes hyperkeratoses, which in turn precede dermal neoplasms. The presence of both hyperpigmentation and palmar-plantar keratoses in the patient suggests that his arsenic exposure began at least 3 years ago, before consumption of drinking water from his current well. Since he resided on nearby property for 10 years, the well at that location should also be suspected of containing high levels of arsenic.

(8) The patient's wife, who resides with the patient and may consume the same well water, is at risk for chronic arsenic poisoning. Residents in the surrounding geographical area, who may also be obtaining water from artesian wells should be considered at risk. Former area residents who consumed arsenic chronically before moving away constitute a third group potentially at risk for delayed development of arsenic-associated disease.

(9) A careful history reveals that the wife, unlike the patient, consumed the well water infrequently, preferring instead to drink bottled soft drinks and juices. Before moving with her husband 10 months ago, she resided in a metropolitan area geographically remote from the present site, where the water was not obtained from wells. Thus, because her arsenic ingestion was markedly lower and of shorter duration than her husband's, she has not yet developed signs or symptoms of chronic arsenic intoxication.

Both the patient and his wife use the arsenic-containing well water for showers and baths. The substantial amount of arsenic in the wife's hair likely reflects external contamination from this source. The arsenic content of the husband's hair is elevated from a combination of external contamination and internal incorporation into the growing hair. The relative contribution from endogenous and exogenous sources cannot be distinguished through bulk hair analysis.

(10) Immediate cessation of consumption of arsenic-containing well water is the essential first step. Because the utility of chelating agents in reversing or improving the patient's arsenic-related peripheral neuropathy, anemia, and palmar-plantar keratoses is unestablished, chelation treatment cannot be routinely recommended. Analgesics and/or certain tricyclic antidepressants have been reported to be beneficial for the painful dysesthesias associated with peripheral neuropathies. Because some reports indicate that vitamin A analogs (retinoids) may be valuable in the treatment of precancerous arsenical keratoses, referral to a dermatologist for consideration of this treatment is indicated. The patient will remain at risk for the delayed appearance of arsenic-related skin cancer and merits regular, long-term dermatologic follow-up.

(11) Because of the likelihood that other wells in the area contain elevated levels of arsenic, public health intervention may be necessary to prevent other cases of hazardous arsenic exposure.

Sources of Information

More information on the adverse effects of arsenic and the treatment and management of arsenic-exposed persons can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Arsenic Toxicity* is one of a series. For other publications in this series, please use the order form on the back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of Director, at (404) 639-6204.

Posttest

Continuing education credit is available to health professionals who use this monograph and complete the posttest. The criterion for awarding CME credits and CEUs is a posttest score of 70% or better.

The Centers for Disease Control (CDC) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians, and by the Council on the Continuing Education Unit (CCEU) to sponsor continuing education units for other health professionals.

The Agency for Toxic Substances and Disease Registry, in joint sponsorship with CDC, is offering 1 credit hour of continuing medical education (CME) credit in category 1 of the Physician's Recognition Award of the American Medical Association and 0.1 hour of continuing education units (CEU) for other health professionals upon completion of this monograph.

This program has been reviewed and is acceptable for 1 prescribed hour by the American Academy of Family Physicians (term of approval: through March 16, 1991). For specific information, please consult the AAFP Office of Continuing Medical Education.

The American College of Emergency Physicians (ACEP) has approved this program for 1 hour of ACEP Category 1 credit.

The American Osteopathic Association (AOA) has approved this program for 1 credit hour of Category 2-B AOA-CME credit.

To receive continuing education credit (CME or CEUs), complete the Posttest on page 26 in the manner shown in the sample question below. **Circle all correct answers.**

Which of the following is known to precipitate migraine headaches?

(a) fatigue
(b) alcohol
c. grapefruit
(d) sunlight
e. sleep

After you have finished the Posttest, please transfer your answers to the answer sheet on the inside back cover and complete the evaluation on the lower half of that page. Fold, staple, and mail the back cover to Continuing Education Coordinator, Agency for Toxic Substances and Disease Registry, Division of Health Education, E33, 1600 Clifton Road, Atlanta, GA 30333. Your confidential test score will be returned with an indication of where the correct answers can be found in the text. Validation of earned CME credit and CEUs will also be forwarded to participants, and their names, if requested, will be placed on the mailing list to receive other issues in the *Case Studies in Environmental Medicine* series.

POSTTEST: ARSENIC

Circle **all** correct answers and transfer your answers to page 27.

1. Arsenic has been used to treat
   a. diarrhea
   b. psoriasis
   c. heart disease
   d. thyroid disease
   e. syphilis
2. Workers who may be exposed to arsenic include
   a. smelter workers
   b. rubber workers
   c. stonemasons
   d. farmers
   e. schoolteachers
3. Clinical signs that may occur in persons with cases of chronic arsenic poisoning include
   a. encephalopathy
   b. sensorimotor peripheral neuropathy
   c. arthritis
   d. anemia
   e. palmar-plantar keratoses
4. In the diagnosis of arsenic poisoning
   a. neurologic findings may be the first diagnostic clue
   b. hyperpigmentation is associated with chronic intoxication
   c. acute hemolysis may indicate arsine gas poisoning
   d. Mees lines may be visible a day after acute exposure
   e. lung and skin cancer may occur
5. Findings that may be encountered in arsenic intoxication include
   a. elevated serum transaminases
   b. hypoglycemia
   c. relative eosinophilia
   d. anemia
   e. hypercalcemia
6. Measures that may be necessary in the treatment of acute arsenic poisoning include
   a. hemodialysis if renal failure occurs
   b. parenteral chelation therapy with dimercaprol (BAL)
   c. fluid replacement therapy with hemodynamic monitoring
   d. hemoperfusion using an ion exchange resin
   e. oral chelation therapy with Prussian blue
7. Some of the more likely activities for exposure to arsenic are
   a. using an indoor firing range
   b. eating seafood
   c. manufacturing silicon wafers or computer chips
   d. sewing textiles
   e. preparing blue prints
8. Which of the following statements are true?
   a. pentavalent arsenic is excreted primarily in feces
   b. arsenic undergoes methylation *in vivo*
   c. spinach contains a high amount of arsenic
   d. trivalent arsenic cannot cross either the blood-brain or placental barriers
   e. arsenic binds to the sulfhydryl groups of proteins

CASE STUDIES IN ENVIRONMENTAL MEDICINE: ARSENIC TOXICITY

If you wish CME credits or CEUs, please indicate your answers to the Posttest questions on page 26 by circling the letters below for the correct answers. Complete the evaluation questionnaire and fill in the information requested on the reverse side. Tear off this last page, fold, staple, and mail to Continuing Education Coordinator, Agency for Toxic Substances and Disease Registry, Division of Health Education, E33, 1600 Clifton Road, Atlanta, GA 30333.

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8. a b c d e

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Please complete the following evaluation by circling your response.

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   Yes No Undecided

2. Was the amount of detail appropriate?

   Too technical Just right Not technical enough

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   Yes No Undecided Not applicable

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- ☐ polyaromatic hydrocarbons (PAHs)
- ☐ polychlorinated biphenyls (PCBs)
- ☐ radon
- ☐ tetrachloroethylene
- ☐ trichloroethylene
- ☐ vinyl chloride

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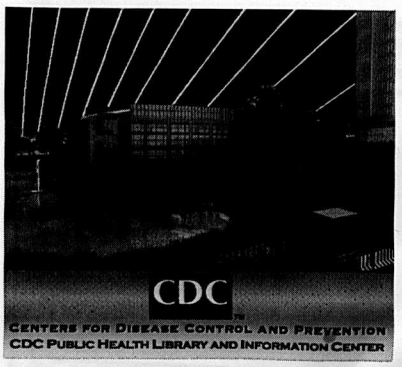

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